

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Rene Gantier et al.                      Art Unit : 1631  
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Title : RATIONAL EVOLUTION OF CYTOKINES FOR HIGHER STABILITY,  
THE CYTOKINES AND ENCODING NUCLEIC ACID MOLECULES

**Appendix**



Cytokine regions susceptible to protease attack identified by structural alignment with Lead mutants of IFN  $\alpha$ -2b

IFN- $\alpha$ 2b	CDLPQTHSLGSRRTLMLLAQMR <sup>R</sup> YISLFSCLKDRHDFGPPQEEFGNQFQKAETIPVLHEMIQQIFNLFSTKDSAAWDETLDDKFTYELYQQLNDEACVIQG VGVTETPLMKEDSILAVRKYFQRTITLYLKEKRYSPCANEVVRRAEIMRSFSLSLTNQLQESLR <sup>SKE</sup>
Exemplary protein of the interferons/interleukin-10 family	
IFN- $\beta$	MSYNLLGFLQRSSNFQCOKLLWQLNGRLEYCLKDRMNF <sup>DIPEEIKQLQQFQKEDAA</sup> LT <sup>IYEMLQNI</sup> FAIFRQDSSTGWN <sup>ET</sup> I <sup>VENLLANVYHQINHLKTVLEEK</sup> LEKED <sup>FTRGKLMSSLHLKRYYGRI</sup> LH <sup>YLKAKEYSHCAWTIVRVEILRN</sup> FYFINRL <sup>TGYLRN</sup>
Exemplary protein of the short-chain cytokines family	
EPO	APRLICDSRVLERYLLEAKEAENITTGCAEHC <sup>SLNENITVPD</sup> TK <sup>VNFYAMKRM</sup> EVGQAVEVWQGL <sup>ALLSEAVLRGQALLVNSSQ</sup> PWEPLQLHVDKAVSGLRSL TTLLRALGAQKEAISP <sup>PPDAASAAPLR</sup> TTITAD <sup>TFRKLF</sup> RVYSN <sup>FLRGK</sup> LKLYTGEA <sup>CRTGDR</sup>
Exemplary protein of the long-chain cytokines family	
G-CSF	TPLGASSLPQSFLLKCLEQVRKIQGDGAALQEKLVSECATYKLC <sup>HPEELVLLGHSLGIPWAPLSSCP</sup> SQALQAGCL <sup>SQ</sup> HSGL <sup>FLYQGLLQALEGISPEL</sup> GPTLDTLQ <sup>L</sup> DVADFATTIWQQMEEL <sup>GMAPALQPTQ</sup> GAMP <sup>AFASAFQRRAGG</sup> VLVASHLQSFLEVS <sup>YRVLRH</sup> LAQ <sup>P</sup>

FIG. 9

